HBV infection likely include a broad and robust antigen-specific T cell response, as well as the development of neutralizing anti-HBs antibodies mediating HBsAg clearance and lifelong protective immunity (Bertoletti and Ferrari, 2016; Corti et al., 2018).

Neutralizing antibodies produced in response to HBV infection target all 3 HBsAg forms. They recognize either the S-HBs antigenic loop and interfere with the pre-attachment to heparane sulfate proteoglycans (HS) on hepatocytes, or the preS1 domain of the L-HBs and block the binding to the host cellular receptor, the sodium taurocholate co-transporting polypeptide (NTCP) (Corti et al., 2018). IgG antibodies against the "*a determinant"* part of the S-HBs loop induced by HBV vaccination (based on recombinant S-HBs immunogens), or administrated to individuals at risk of exposure by polyclonal HBV immunoglobulin infusions confer protection against HBV infection (Samuel et al., 1993; West and Calandra, 1996). Several neutralizing anti-preS and anti-S-HBs antibodies have been isolated from immunized mice and from few human immune donors (Corti et al., 2018). S-HBs neutralizing antibodies may contribute to the viral clearance and long-term suppression in HBV seroconverters as they do for protecting vaccinees from infection. However, no studies have been performed on the memory B-cell response to HBV in functionally cured HBV-infected individuals by cloning and charactering human HBsAg-specific antibodies.

SUMMARY

The disclosure provides anti-S-HBs antibodies and methods of using the same.

In one aspect, the present disclosure provides an antibody that binds to S-HBs, wherein the antibody comprises

a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:1, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:2, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:3, and

a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:4, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:5, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:6.

In another aspect, the present disclosure provides an isolated nucleic acid encoding the antibody as described herein.

In another aspect, the present disclosure provides a host cell comprising the nucleic acid as described herein.

In another aspect, the present disclosure provides a method of producing an antibody that binds to S-HBs comprising culturing the host cell as described herein under conditions suitable for the expression of the antibody, optionally further comprising recovering the antibody from the host cell.

In another aspect, the present disclosure provides an antibody produced by the method as described herein.

In another aspect, the present disclosure provides a pharmaceutical composition comprising the antibody as described herein and a pharmaceutically acceptable carrier.

In another aspect, the present disclosure provides the antibody as described herein or the pharmaceutical composition as described herein, for use as a medicament.

In another aspect, the present disclosure provides the antibody as described herein or the pharmaceutical composition as described herein, for use in treating hepatitis B.

In another aspect, the present disclosure provides the antibody as described herein or the pharmaceutical composition as described herein, for use in treating hepatitis B, wherein an additional therapeutic agent is to be further administered.

In another aspect, the present disclosure provides a therapeutic agent selected from INFα; a therapeutic vaccine; a TLR agonist; and/or a checkpoint inhibitor, for use in treating hepatitis B, wherein the antibody as described herein or the pharmaceutical composition as described herein is to be further administered.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. S-HBs memory antibodies cloned from HBV vaccinees and controllers

(**A**) Average S-HBsAg-reactivity of serum IgGs from HBV vaccinees (HBVv, n=6, bottom curve) and controllers (HBVc, n=8, top curve). Shaded regions indicate value ranges. Representative flow-cytometry plots showing S-HBs-binding IgG^+ memory B cells in HBV vaccinees and controllers (Bv4 and Bc3 are shown). nS-HBsAg and rS-HBsAg are human-derived native and recombinant S-HBs antigens, respectively.

WHAT IS CLAIMED IS:

1. An antibody that binds to S-HBs, wherein the antibody comprises

a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:1, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:2, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:3, and

a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:4, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:5, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:6.

2. The antibody of claim 1, comprising a sequence selected from the group consisting of

(a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:16;

(b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:15; and

(c) a VH sequence as defined in (a) and a VL sequence as defined in (b).

3. The antibody of claim 1 or claim 2, comprising a VH sequence of SEQ ID NO: 16 and a VL sequence of SEQ ID NO: 15.

4. The antibody according to any one of claims 1 to 3, which is cross-reactive against each of the HBV proteins of SEQ ID NO: 254 to 262.

5. The antibody according to any one of claims 1 to 4, which has neutralizing activity against a genome D HBV in vivo or in vitro, optionally which has a neutralizing IC50 value against HBV genome D of ≤1ng/ml, measured in vitro.

6. The antibody of any one of claims 1 to 5, which is a monoclonal antibody.

7. The antibody of any one of claims 1 to 6, which is a human or chimeric antibody.

8. The antibody of any one of claims 1 to 7, which is an antibody fragment that binds S-HBs.

9. The antibody of any one of claims 1 to 7, which is a full-length IgG antibody.

10. The antibody of any one of claims 1 to 3 comprising a heavy chain of SEQ ID NO:18 or 263 and a light chain of SEQ ID NO:17.

11. The antibody of claim 9, comprising an Fc region with one or more substitutions therein which improve binding of the Fc region to FcRn.

12. The antibody of claim 11, wherein said substitutions are selected from the group consisting of:

i) M252Y, S254T and T256E;

ii) M428L, N434A and Y436T;

iii) N434A; and

iv) T307H and N434H,

optionally wherein the antibody comprises a light chain of SEQ ID NO: 17 and a heavy chain of SEQ ID NO: 18 or 263 modified by one or more substitutions selected from the group consisting of:

i) M252Y, S254T and T256E;

ii) M428L, N434A and Y436T;

iii) N434A; and

iv) T307H and N434H.

13. An isolated nucleic acid encoding the antibody of any one of claims 1 to 12.

14. A host cell comprising the nucleic acid of claim 13.

15. A method of producing an antibody that binds to S-HBs comprising culturing the host cell of claim 14 under conditions suitable for the expression of the antibody, optionally further comprising recovering the antibody from the host cell.

16. An antibody produced by the method of claim 15.

17. A pharmaceutical composition comprising the antibody of any one of claims 1 to 12 or claim 16 and a pharmaceutically acceptable carrier.

18. The pharmaceutical composition of claim 17, further comprising an additional therapeutic agent.

19. The antibody of any one of claims 1 to 12 or claim 16 or the pharmaceutical composition of claim 17 or claim 18, for use as a medicament.

20. The antibody of any one of claims 1 to 12 or claim 16 or the pharmaceutical composition of claim 17 or 18, for use in treating hepatitis B.

21. The antibody of any one of claims 1 to 12 or claim 16 or the pharmaceutical composition of claim 17, for use in treating hepatitis B, wherein an additional therapeutic agent is to be further administered.

22. The pharmaceutical composition according to claim 18 or the antibody or pharmaceutical composition for use according to claim 21, wherein the additional therapeutic agent is selected from the group consisting of: an siRNA targeted to an HBV sequence; a nucleotide analog reverse-transcriptase inhibitor or a nucleoside analogue; INFα or pegylated IFN-α; a therapeutic vaccine; a TLR agonist; and/or a checkpoint inhibitor.

23. A therapeutic agent selected from INFα; a therapeutic vaccine; a TLR agonist; and/or a checkpoint inhibitor, for use in treating hepatitis B, wherein the antibody according to any one of claims 1 to 12 or claim 16 or the pharmaceutical composition of claim 17 is to be further administered.

24. The antibody or pharmaceutical composition for use according to any one of claims 19 to 22 or therapeutic agent for use according to claim 23, wherein said hepatitis B is chronic hepatitis B.

***